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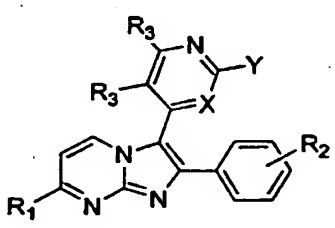
(54) Title: SUBSTITUTED 2-ARYL-3-(HETEROARYL)-IMIDAZO[1,2-*a*]PYRIMIDINES, AND RELATED PHARMACEUTICAL COMPOSITIONS AND METHODS



(I)

(57) Abstract: This invention relates to a series of imidazopyrimidines of Formula (I), and pharmaceutical compositions containing them. The compounds of the invention inhibit the production of a number of inflammatory cytokines and are useful in the treatment and prevention of diseases associated with the overproduction thereof.

SUBSTITUTED 2-ARYL-3-(HETEROARYL)-IMIDAZO[1,2-a]PYRIMIDINES, AND RELATED PHARMACEUTICAL COMPOSITIONS AND METHODS

Field of the Invention

This invention relates to a series of substituted imidazopyrimidines and pharmaceutical compositions containing them. The compounds of the invention inhibit the production of a number of inflammatory cytokines, particularly TNF-α and IL-1β. Compounds of this invention are useful in the treatment of diseases mediated by p38, such as rheumatoid arthritis, inflammatory bowel disease, septic shock, osteoporosis, osteoarthritis, neurodegenerative disorders, and AIDS-related diseases.

Background of the Invention

The inflammatory cytokines TNF-α and IL-1β play an important role in a number of inflammatory diseases such as rheumatoid arthritis (Dinarello et al., Curr. Opin. Immunol., 1991, 3: 941-8). Arthritis is an inflammatory disease which affects millions of people and can strike at any joint in the human body. Its symptoms range from mild pain and inflammation in affected joints, to severe and debilitating pain and inflammation. Although the disease is associated mainly with aging adults, it is not restricted to adults.

The most common arthritis therapy involves the use of nonsteroidal anti-inflammatory drugs ("NSAID's") to alleviate the symptoms. However, despite the widespread use of NSAID's, many individuals cannot tolerate the doses necessary to treat the disease over a prolonged period of time. In addition, NSAID's merely treat the symptoms of the disease without affecting the underlying cause. Other drugs such as methotrexate, D-pencillamine, gold salts, and Frednione are often used when patients fail to respond to NSAID's. These drugs also have significant toxicities and their mechanisms of action remain unknown.

Receptor antagonists to IL-1β and monoclonal antibodies to TNF-α have been shown to reduce symptoms of rheumatoid arthritis in small-scale human clinical trials. In addition to protein-based therapies, there are small molecule agents which inhibit the production of these cytokines and have demonstrated activity in animal arthritis models (Boehm et al., J. Med. Chem., 1996, 39:3929-37). Of these small molecule agents, SB 203580 has proven effective in reducing the production of TNF-α and IL-1 in LPS-stimulated human monocyte cell lines with IC_{50} values of 50 to 100 nM (Adams et al., WO 93/14081, July 23, 1993). In addition to this *in vitro* test, SB 203580 inhibits the production of the inflammatory cytokines in rats and mice at IC_{50} values of 15 to 25 mg/kg (Badger,et al, J. Pharm. Exp. Therap., 1996, 279:1453-61). Although human data are currently unavailable for SB 203580, monoclonal antibodies to TNF-α have proven efficacious in the treatment of rheumatoid arthritis (Elliot et al., Arthritis Rheum. 1993, 36: 1681- 90). Due to SB 203580's oral activity and potency in animal models, researchers have suggested that a compound with this profile has potential as a viable treatment for rheumatoid arthritis (Badger et al., J. Pharm. Exp. Therap., 1996, 279:1453-61).

SB 203580 and other small molecule agents reduce the production of inflammatory cytokines by inhibiting the activity of a serine/threonine kinase p38, which sometimes is referred to as CSBP, at an IC_{50} of 200 nM (Griswold et al., Pharm. Commun., 1996, 7:323-9). Although the precise role of this kinase is unknown, it has been implicated in both the production of TNF-α and the signaling responses associated with the TNF- α receptor.

WO 91/00092 discloses a method of inhibiting the production of interleukin-1 by monocytes and/or macrophages in humans by administering a diaryl-substituted imidazole fused to a second heterocyclic ring containing a nitrogen bridgehead atom, wherein the second ring may also contain sulfur, oxygen or an additional nitrogen atom, and may contain additional unsaturation.

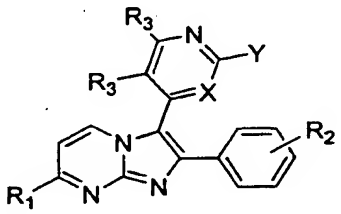
WO 90/15534 and EP 0403251 disclose treatments of humans afflicted with a T Cell Viral (TIV) infection which comprises administering an effective amount of a monokine activity-reducing agent.

WO 91/19497 discloses a diaryl-substituted imidazole compound useful in dual inhibition of 5-lipoxygenase pathway-mediated diseases and cyclooxygenase pathway-mediated diseases. This compound is fused to a second unsaturated 5 or 6 membered heterocyclic ring containing a nitrogen bridgehead atom, wherein the second 5 membered ring also contains a sulfur or oxygen atom and the 6 membered ring may also contain an additional nitrogen atom.

Despite these known compounds and methods, there remains a need in the art for improved methods of reducing inflammatory cytokine production through inhibiting serine/threonine kinase p38 activity, and for related methods of treating and preventing arthritis and other inflammatory disorders.

Summary of the Invention

This invention provides novel compounds which inhibit the *in vitro* activity of p38 in the nanomolar range as well as methods for making same. In addition, the compounds of the present invention inhibit the *in vitro* secretion of TNF-α and IL-1β in the nanomolar range. Animal models demonstrate the inhibition of LPS-induced TNF-α production. Demonstrated to have these biological activities by *in vitro* and *in vivo* assays described hereinafter are the compounds of the present invention as shown in Formula I:



Formula I

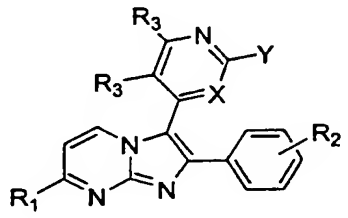
This invention also provides a pharmaceutical composition comprising the instant compound and a pharmaceutically acceptable carrier, as well as related synthetic methods.

This invention further provides a method of treating a subject suffering from a condition whose alleviation is mediated by the reduction of inflammatory cytokines whose actions contribute to the condition, which method comprises administering to the subject a therapeutically effective dose of the instant pharmaceutical composition.

This invention still further provides a method of inhibiting in a subject the onset of a condition whose alleviation is mediated by the reduction of inflammatory cytokines whose actions contribute to the condition, which method comprises administering to the subject a prophylactically effective dose of the instant pharmaceutical composition.

Detailed Description of the Invention

This invention provides a compound of Formula I,



Formula I

or a pharmaceutically acceptable salt thereof, wherein

(a) R_1 is selected from NH_2, C_{1-5}alkylamino, diC_{1-5}alkylamino, hydroxy, C_{1-5}alkoxy, phenylmethylamino, heterocyclylmethyl, C_{1-5}alkylcarbonylamino, and substituted phenylcarbonylamino, wherein

said phenylmethylamino and heterocyclylmethyl may be substituted on its phenyl moiety by one or more members selected from the group consisting of halogen, C_{1-5}alkyl, C_{1-5}alkoxy, arylC_{1-3}alkylamino, R′R″NCH=N- and OR‴, the R′, R″, and R‴ being independently selected from H, C_{1-5}alkyl, phenylmethyl, substituted phenylmethyl, α-alkyl-phenylmethyl, substituted α-alkyl-phenylmethyl, heterocyclylmethyl, and substituted heterocyclylmethyl;

(b) Y is selected from the group consisting of H, halogen, heterocycle, OR_4, SR_4, NR_4, and NR_4R_5, wherein

R_4 and R_5 are independently selected from H, heterocyclyl, C_{3-5} carbocycle, phenyl, α-alkyl-phenylC_{1-5}alkyl, straight or branched alkyl optionally substituted with R, NR, $N(R)_2$, C_{3-5} carbocycle, phenyl or substituted phenyl, wherein (i) R is H, halogen, C_{1-5} alkyl, phenyl methyl, substituted phenyl methyl, SO_2Ph, pyridyl, or pyridyl methyl, and (ii) said phenyl, heterocyclyl, and α-alkyl-phenylC_{1-5}alkyl may be substituted by one or more members selected from the group consisting of halogen, C_{1-}

$_5$alkyl, C_{1-5}alkoxy, arylC_{1-3}alkylamino, phenyl methyl, substituted phenyl methyl, R'R''NCH=N- and OR''' as defined in (a) hereof;

(c) R_2 is one to five members independently selected from the group consisting of halogen, trifluoromethyl, -NCH_2PH, C_{1-5}alkyl, and C_{1-5}alkoxy;

(d) R_3 is H or, taken together, an aromatic ring; and

(e) X is N or CH.

In one embodiment of the instant compound, R_1 is NH_2. In another embodiment, R_2 is a member selected from the group consisting of halogen, trifluoromethyl, -NCH_2PH, and C_{1-5}alkoxy. In yet another embodiment, Y is NR_4 and R_4 is phenylmethyl. In still another embodiment, X is CH.

Unless specified otherwise, the term "alkyl" refers to a straight, branched or cyclic substituent consisting solely of carbon and H with no unsaturation. The term "alkoxy" refers to O-alkyl where alkyl is as defined supra. The term "aromatic ring" refers to a 5- to 6-membered ring containing a 6-electron delocalized conjugated pi bonding system such as phenyl, furanyl, and pyrrolyl. The term "aryl" includes mono and fused aromatic rings such as phenyl, naphthyl, diphenyl, fluorophenyl, difluorophenyl, benzyl, benzoyloxyphenyl, carboethoxyphenyl, acetylphenyl, ethoxyphenyl, phenoxyphenyl, hydroxyphenyl, carboxyphenyl, trifluoromethylphenyl, methoxyethylphenyl, acetamidophenyl, tolyl, xylyl, dimethylcarbamylphenyl and the like. The term "halo" means fluoro, chloro, bromo and iodo. The symbol "Ph" refers to phenyl. The term "heterocyclyl", "heterocycle" or "heterocyclic residue" represents a single or fused ring having at least one atom other than carbon as ring member, e.g. pyridine, pyrimidine, oxazoline, pyrrole, imidazole, morpholine, furan, indole, benzofuran, pyrazole, pyrrolidine, piperidine, and benzimidazole.

Substituted heterocyclylmethyl and substituted phenylmethyl have substituents such as halogen, C_{1-5}alkyl, C_{1-5}alkoxy, arylC_{1-3}alkylamino, R′R″NCH=N-, and OR‴ wherein R′, R″, and R‴ are independently selected from H, C_{1-5}alkyl, phenylmethyl, substituted phenylmethyl, α-alkyl-phenylmethyl and substituted α-alkyl-phenylmethyl, heterocyclylmethyl, and substituted heterocyclylmethyl.

The term "FCS" represents fetal calf serum, "TCA" represents trichloroacetic acid, and "RPMI" represents the medium from the Roswell Park Memorial Inst. (Sigma cat # R0833). "Independently" means that when there is more than one substituent, the substituents may be different. "DME" refers to ethylene glycoldimethyl. The term "NaHMDS" refers to sodium hexamethyldisilazide.

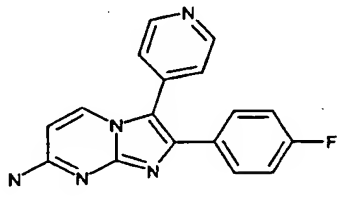
The phrase "pharmaceutically acceptable salt" denotes salts of the free base which possess the desired pharmacological activity of the free base and which are neither biologically nor otherwise undesirable. These salts may be derived from inorganic or organic acids. Examples of inorganic acids are hydrochloric acid, hydrobromic acid, hydroiodic acid, perchloric acid, nitric acid, sulfuric acid and phosphoric acid. Examples of organic acids are acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, malic acid, maleic acid, maieic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, oxalic acid, pamoic acid, saccharic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, methyl sulfonic acid, salicyclic acid, hydroethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, cyclohexanesulfamic acid and the like.

Where the compounds according to this invention have one or more stereogenic centers, it is to be understood that all possible optical isomers, antipodes, enantiomers, and diastereomers resulting from additional stereogenic centers that may exist in optical antipodes, racemates and racemic mixtures thereof are also part of this invention. The antipodes can be

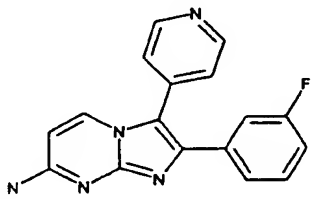
separated by methods known to those skilled in the art such as, for example, fractional recrystallization of diastereomeric salts of enantiomerically pure acids. Alternatively, the antipodes can be separated by chromatography in a Pirkle-type column.

The following compounds are exemplary of the present invention:

Compound 1: 2-(4-fluorophenyl)-3-(4-pyridinyl)-imidazo[1,2-*a*]pyrimidin-7-amine;



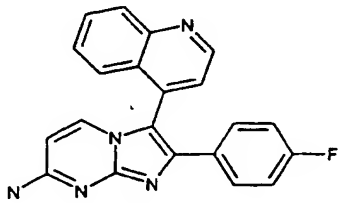
Compound 1



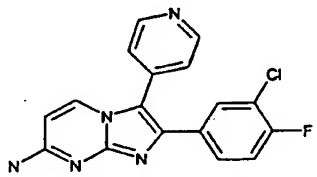
Compound 2

Compound 2: 2-(3-fluorophenyl)-3-(4-pyridinyl)-imidazo[1,2-*a*]pyrimidin-7-amine;

Compound 3: 2-(4-fluorophenyl)-3-(4-quinolinyl)-imidazo[1,2-*a*]pyrimidin-7-amine;



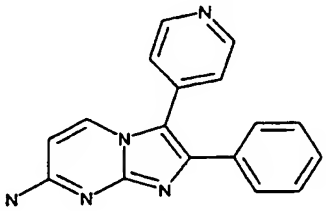
Compound 3



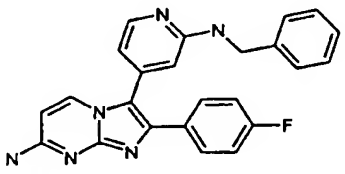
Compound 4

Compound 4: 2-(3-chloro-4-fluorophenyl)-3-(4-pyridinyl)-imidazo[1,2-*a*]pyrimidin-7-amine;

Compound 5: 2-phenyl-3-(4-pyridinyl)-imidazo[1,2-*a*]pyrimidin-7-amine;



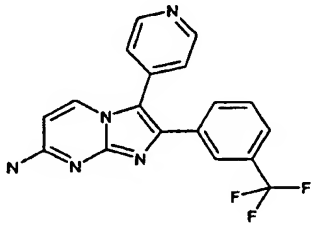
Compound 5



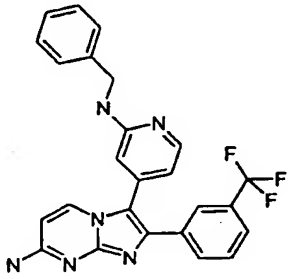
Compound 6

Compound 6: 2-(4-fluorophenyl)-3-[2-[(phenylmethyl)amino]-4-pyridinyl]-imidazo[1,2-*a*]pyrimidin-7-amine;

Compound 7: 3-(4-pyridinyl)-2-[3-(trifluoromethyl)phenyl]-imidazo[1,2-*a*]pyrimidin-7-amine;



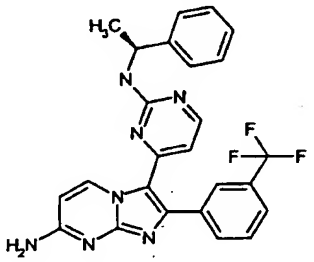
Compound 7



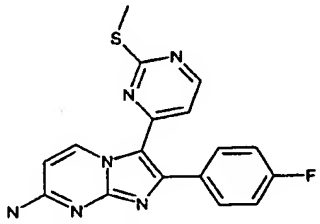
Compound 8

Compound 8: 3-[2-[(phenylmethyl)amino]-4-pyridinyl]-2-[3-(trifluoromethyl)phenyl]-imidazo[1,2-*a*]pyrimidin-7-amine;

Compound 9: 3-[2-[[(1*S*)-1-Phenylethyl]amino]-4-pyrimidinyl]-2-[3-(trifluoromethyl)phenyl]imidazo[1,2-*a*]pyrimidin-7-amine;



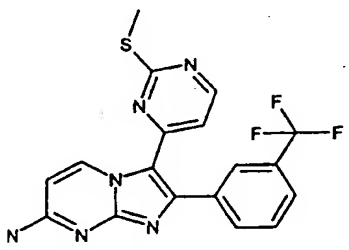
Compound 9



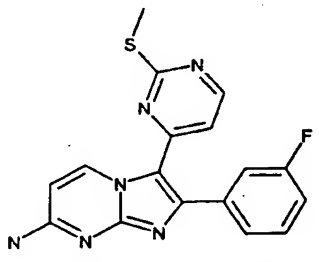
Compound 10

Compound 10: 2-(4-Fluorophenyl)-3-[2-(methylthio)-4-pyrimidinyl] imidazo[1,2-*a*]pyrimidin-7-amine;

Compound 11: 3-[2-(Methylthio)-4-pyrimidinyl]-2-[3-(trifluoromethyl) phenyl]imidazo[1,2-*a*]pyrimidin-7-amine;



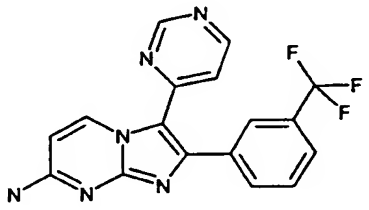
Compound 11



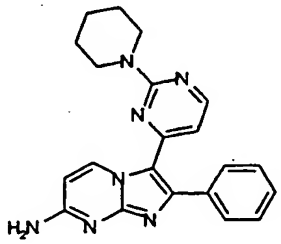
Compound 12

Compound 12: 2-(3-Fluorophenyl)-3-[2-(methylthio)-4-pyrimidinyl] imidazo[1,2-*a*]pyrimidin-7-amine;

Compound 13: 3-(4-Pyrimidinyl)-2-[3-(trifluoromethyl)phenyl] imidazo[1,2-*a*]pyrimidin-7-amine;



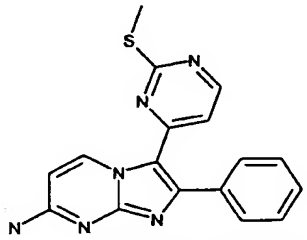
Compound 13



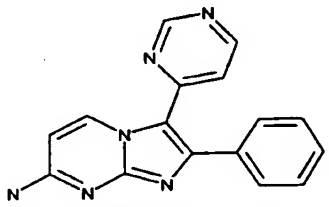
Compound 14

Compound 14: 2-Phenyl-3-[2-(1-piperidinyl)-4-pyrimidinyl]imidazo[1,2-*a*]pyrimidin-7-amine;

Compound 15: 3-[2-(Methylthio)-4-pyrimidinyl]-2-phenylimidazo[1,2-*a*]pyrimidin-7-amine;



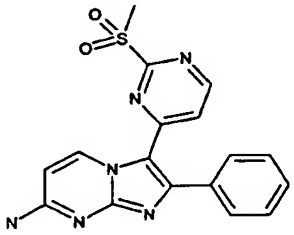
Compound 15



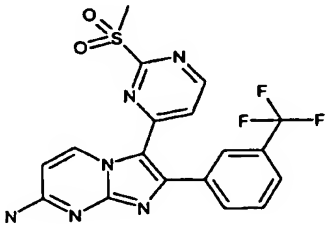
Compound 16

Compound 16: 2-Phenyl-3-(4-pyrimidinyl)imidazo[1,2-*a*]pyrimidin-7-amine;

Compound 17: 3-[2-(Methylsulfonyl)-4-pyrimidinyl]-2-phenylimidazo [1,2-*a*]pyrimidin-7-amine;



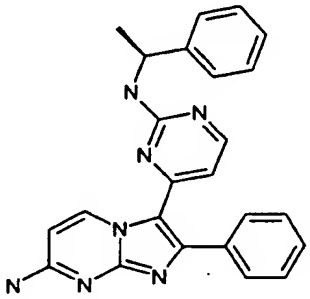
Compound 17



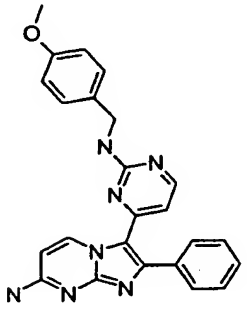
Compound 18

Compound 18: 3-[2-(Methylsulfonyl)-4-pyrimidinyl]-2-[3-(trifluoromethyl)phenyl]imidazo[1,2-*a*]pyrimidin-7-amine;

Compound 19: 2-Phenyl-3-[2-[[(1*S*)-1-phenylethyl]amino]-4-pyrimidinyl]imidazo[1,2-*a*]pyrimidin-7-amine;



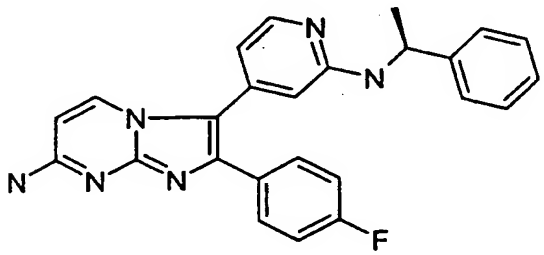
Compound 19



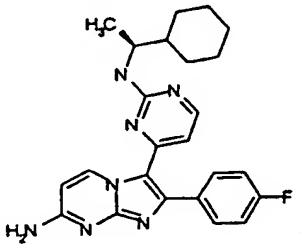
Compound 20

Compound 20: 3-[[[(4-Methoxyphenyl)methyl]amino]-4-pyrimidinyl]-2-phenylimidazo[1,2-*a*]pyrimidin-7-amine;

Compound 21: 2-(4-Fluorophenyl)-3-[3-[[(1*S*)-1-phenylethyl]amino]-4-pyridinyl]imidazo[1,2-*a*]pyrimidin-7-amine;



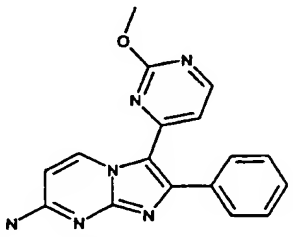
Compound 21



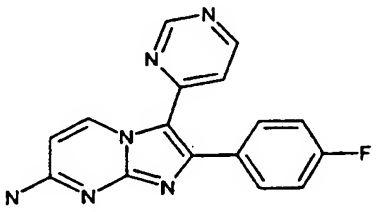
Compound 22

Compound 22: 3-[2-[[(1*S*)-1-Cyclohexylethyl]amino]-4-pyrimidinyl]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyrimidin-7-amine;

Compound 23: 3-(2-Methoxy-4-pyrimidinyl)-2-phenylimidazo[1,2-*a*]pyrimidin-7-amine;



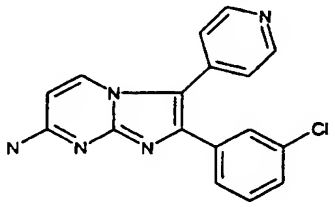
Compound 23



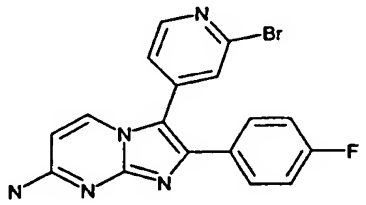
Compound 24

Compound 24: 2-(4-Fluorophenyl)-3-(4-pyrimidinyl)imidazo[1,2-*a*]pyrimidin-7-amine;

Compound 25: 2-(3-Chlorophenyl)-3-(4-pyridinyl)imidazo[1,2-*a*]pyrimidin-7-amine;



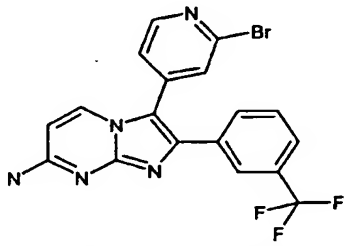
Compound 25



Compound 26

Compound 26: 3-(2-Bromo-4-pyridinyl)-2-(4-fluorophenyl)imidazo[1,2-*a*]pyrimidin-7-amine; and

Compound 27: 3-(2-Bromo-4-pyridinyl)-2-[3-(trifluoromethyl)phenyl] imidazo[1,2-*a*]pyrimidin-7-amine.



Compound 27

This invention also provides a pharmaceutical composition comprising the instant compound and a pharmaceutically acceptable carrier.

Pharmaceutical compositions containing the compound of the present invention as the active ingredient in intimate admixture with a pharmaceutical carrier can be prepared according to conventional pharmaceutical techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, such as topical administration and systemic administration including, but not limited to, intravenous infusion, oral, nasal or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical carriers may be employed, such as water, glycerol,

glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, syrup and the like in the case of oral liquid preparations (for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, methyl cellulose, magnesium sterate, dicalcium phosphate, mannitol and the like in the case of oral solid preparations (for example, powders, capsules and tablets). All excipients may be mixed as needed with disintegrants, diluents, granulating agents, lubricants, binders and the like using conventional techniques known to those skilled in the art of preparing dosage forms.

The preferred route of administration is oral administration. Because of their ease in administration, tablets and capsules represent an advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, to aid solubility or for preservative purposes, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed.

As used in this invention, the term "cytokine" refers to the proteins TNF-α and IL-1β. Cytokine-related disorders are diseases of humans and other mammals where the overproduction of cytokines causes the symptoms of the disease. The overproduction of the cytokines TNF- α and IL-1β has been linked to a number of diseases.

The compounds of the present invention inhibit the production of TNF-α and IL-1β. Thus, this invention further provides a method of treating a subject suffering from a condition whose alleviation is mediated by the reduction of inflammatory cytokines whose actions contribute to the condition, which method comprises administering to the subject a therapeutically effective dose of the instant pharmaceutical composition. As used herein, the term "subject" includes, without limitation, any animal or artificially modified animal. In the preferred embodiment, the subject is a human.

This invention still further provides a method of inhibiting in a subject the onset of a condition whose alleviation is mediated by the reduction of inflammatory cytokines whose actions contribute to the condition, which method comprises administering to the subject a prophylactically effective dose of the instant pharmaceutical composition.

In one embodiment, the condition is selected from the group consisting of arthritis, inflammatory bowel disease, septic shock, osteoporosis, osteoarthritis, neuropathic pain, HIV replication, HIV dementia, viral myocarditis, insulin-dependent diabetes, non-insulin dependent diabetes, periodontal disease, restenosis, alopecia areta, T-cell depletion in HIV infection or AIDS, psoriasis, acute pancreatitis, allograft rejection, allergic inflammation in the lung, atherosclerosis, multiple sclerosis, cachexia, Alzheimer's disease, stroke, Crohn's disease, ischemia, congestive heart failure, pulmonary fibrosis, hepatitis, glioblastoma, Guillain-Barre Syndrome, and systemic lupus erythematosus. In the preferred embodiment, the condition is rheumatoid arthritis

As used herein, "treating" a disorder means eliminating or otherwise ameliorating the cause and/or effects thereof. "Inhibiting" the onset of a disorder means preventing, delaying or reducing the likelihood of such onset. Likewise, "therapeutically effective" and "prophylactically effective" doses are doses that permit the treatment and inhibition, respectively, of a disorder. Methods are known in the art for determining therapeutically and prophylactically effective doses for the instant pharmaceutical composition. The effective dose for administering the pharmaceutical composition to a human, for example, can be determined mathematically from the results of animal studies.

In one embodiment, oral doses of the instant compounds range from about 0.05 to about 100 mg/kg, daily. In another embodiment, oral doses range from about 0.05 to about 50 mg/kg daily, and in a further embodiment,

from about 0.05 to about 20 mg/kg daily. Infusion doses can range, for example, from about 1.0 to 1.0 X 10^4 μg/kg/min of instant compound, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days. For topical administration, the instant compound can be mixed with a pharmaceutical carrier at a concentration of, for example, about 0.1 to about 10% of drug to vehicle.

Finally, this invention provides processes for preparing the instant compounds. These compounds can be prepared as shown below from readily available starting materials and/or intermediates following processes well known in the art.

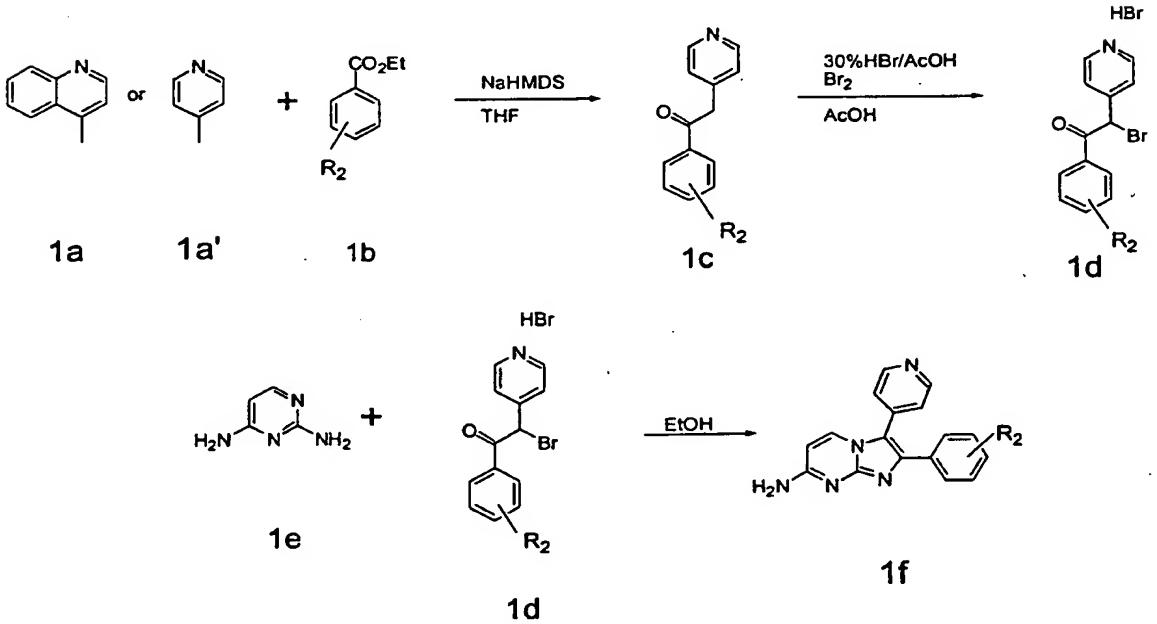
This invention will be better understood by reference to the Experimental Details that follow, but those skilled in the art will readily appreciate that these are only illustrative of the invention as described more fully in the claims which follow thereafter. Additionally, throughout this application, various publications are cited. The disclosure of these publications is hereby incorporated by reference into this application to describe more fully the state of the art to which this invention pertains.

Experimental Details

A. Schemes and Syntheses

Compounds of Formula I in which R_1 is NH_2, and R_3 and Y are H may be prepared by Scheme I. A starting compound of type 1a, such as 4-methyl pyridine or 4-methyl quinoline, may be stirred with a benzoic ester of type 1b and two equivalents of a suitable hindered base, such as sodium hexamethyldisiiazide in a suitable solvent such as THF at room temperature to give the enolate of 1c which is then brominated to type 1d. An intermediate of type 1d may be further reacted with 2,6-diaminopyrimidine to give a compound of Formula I in which R_1 is NH_2 and Y is H.

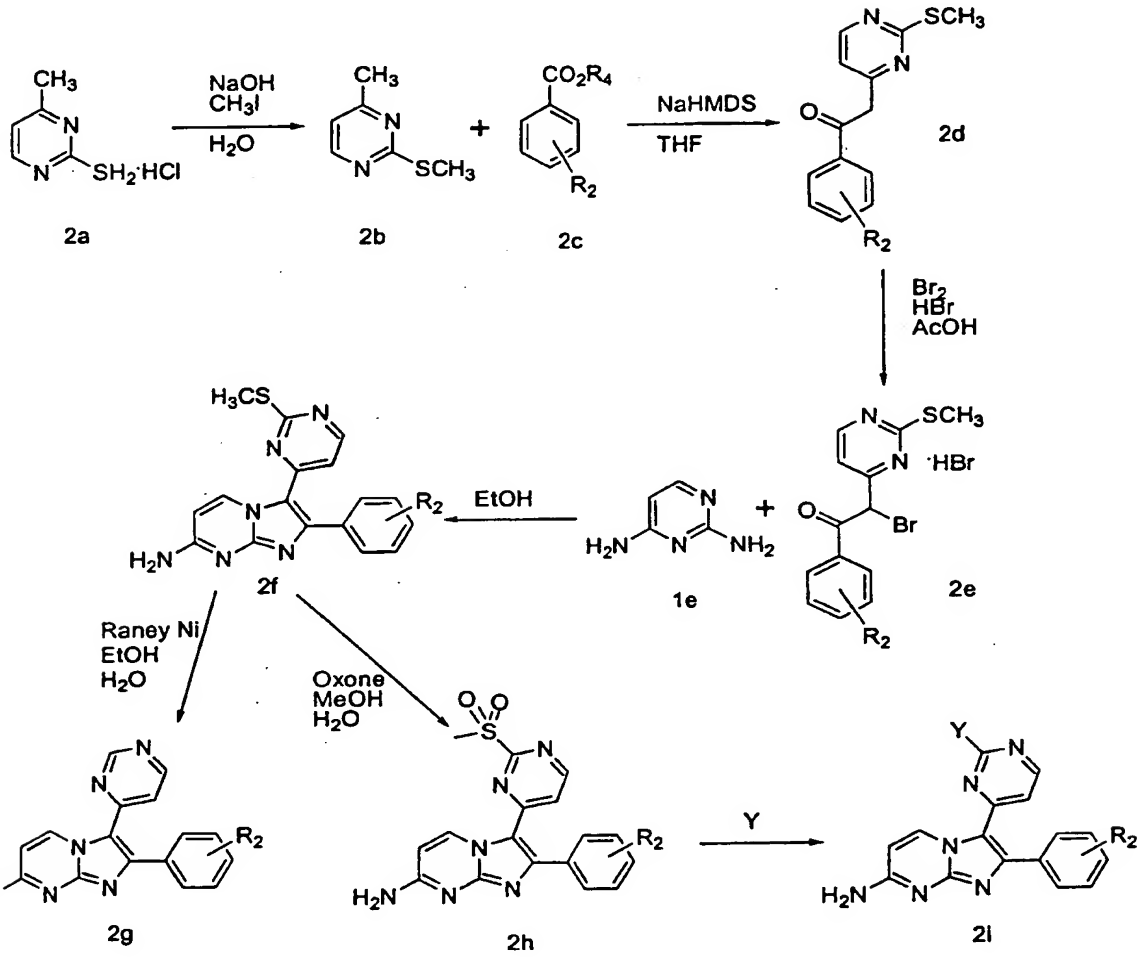
SCHEME I



Although the illustrated method produces a compound of Formula I where R_1 is NH_2, X is CH, and Y is H, this scheme may also be used to produce other compounds of the invention.

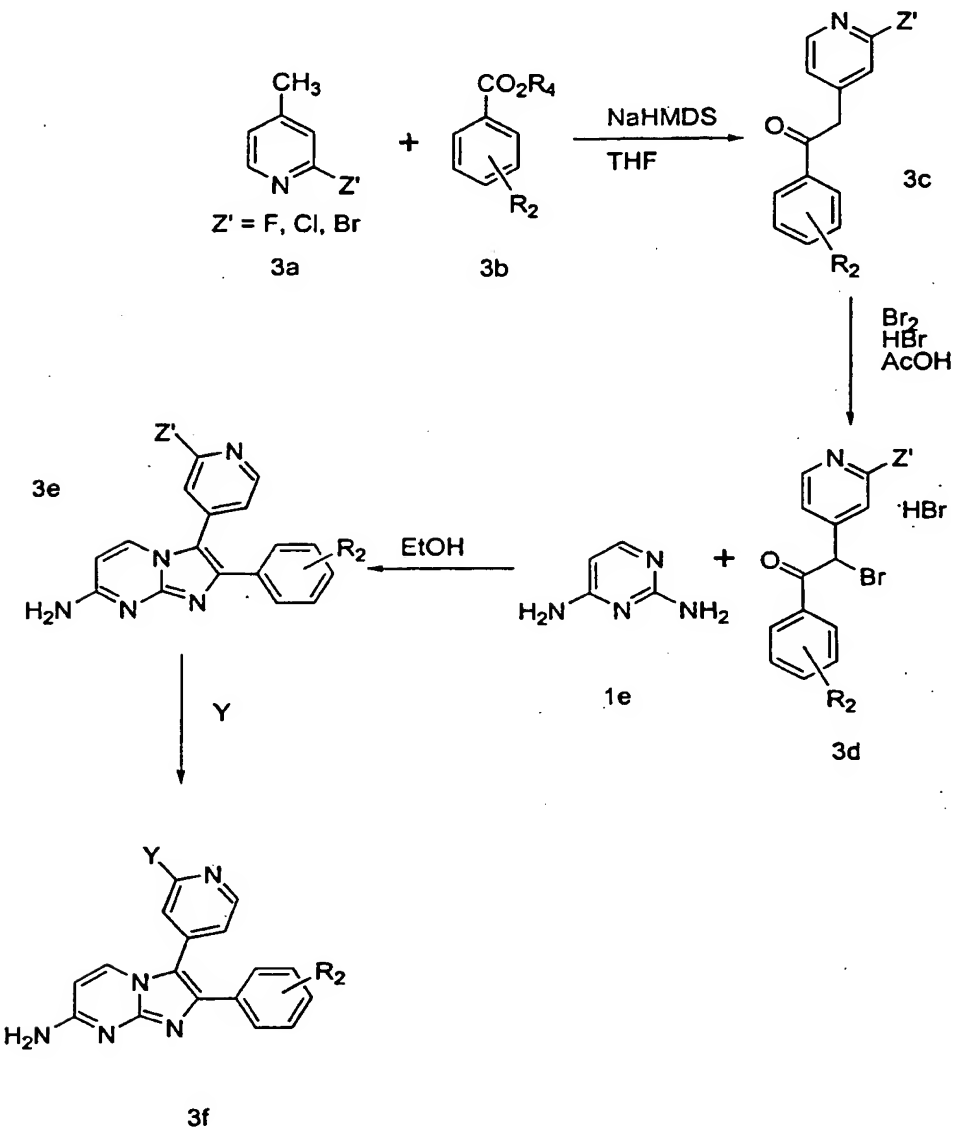
Scheme II shows how to make compounds of Formula I wherein X is N, and Y, R_2 and R_3 are defined as hereinabove.

SCHEME II



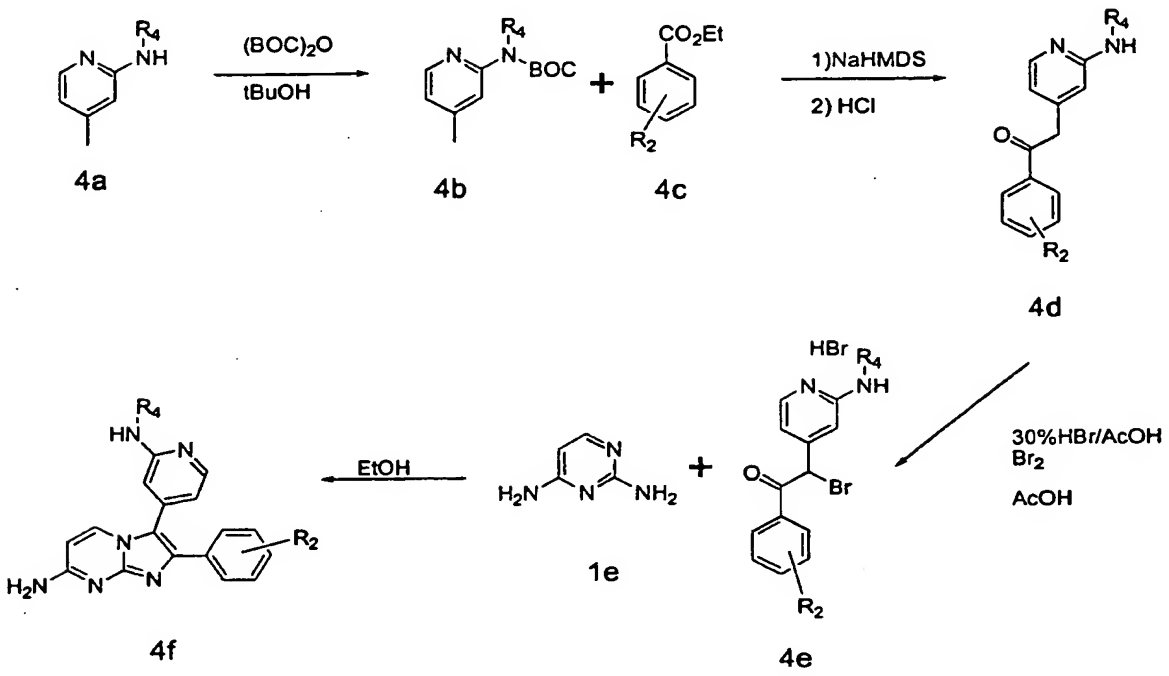
Scheme III shows how to make compounds of Formula I wherein X is CH, Z' is F, Cl or Br, and Y, R_2 and R_3 are as defined hereinabove.

SCHEME III



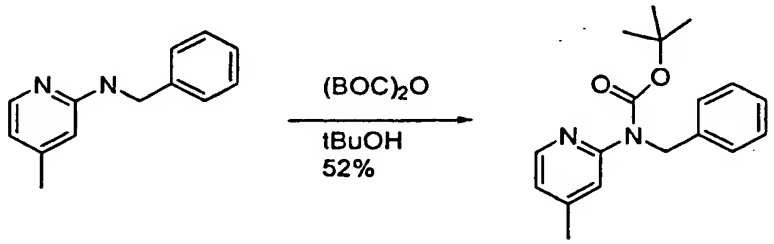
Scheme IV shows how to make compounds of Formula I wherein X is CH, Y is NR_4 and R_4 is defined as hereinabove.

SCHEME IV

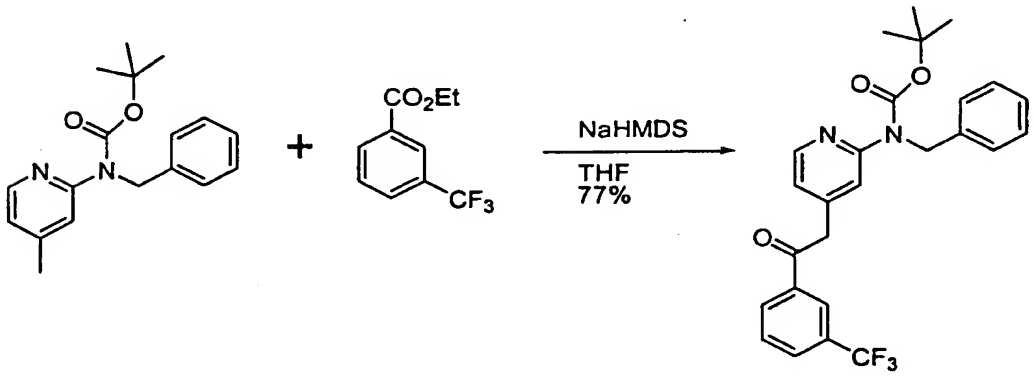


The examples below describe in greater particularity the chemical synthesis of representative compounds of the present invention. The remaining compounds disclosed herein can be prepared similarly in accordance with one or more of these methods. No attempt has been made to optimize the yields obtained in these reactions, and it would be clear to one skilled in the art that variations in reaction times, temperatures, solvents, and/or reagents could increase such yields.

Example 1
Imidazo[1,2-*a*]pyrimidin-7-amine, 3-[2-[(phenylmethyl)amino]-4-pyridinyl]-2-[3-(trifluoromethyl)phenyl]

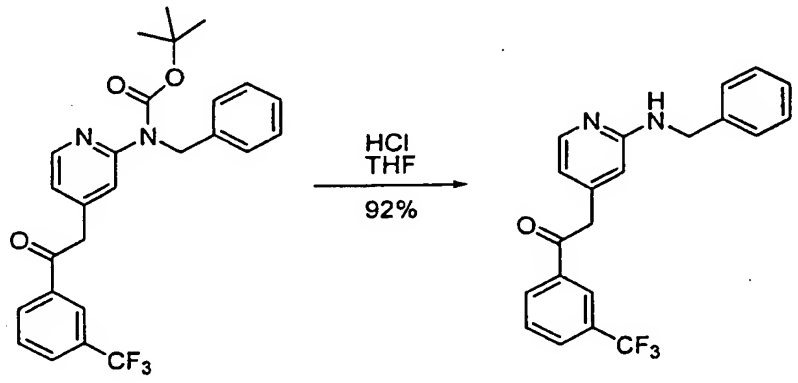


6.59g (31.18 mmoles) of Di-t-butyldicarbonate was added to 5.44g (27.44 mmoles) of 2-benyzlamino-4-methylpyridine in 40ml t-butanol. After 18 hours the solvent was removed *in vacuo*. The residue was triturated with hexane and filtered. The filtrate was concentrated *in vacuo* to give 4.25g of the protected amine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (1H, d, J=5.1 Hz), 6.99 (1H, d, J=5.1 Hz), 5.10 (2H, s), 2.31 (3H,s), 1.38 (9H,s).

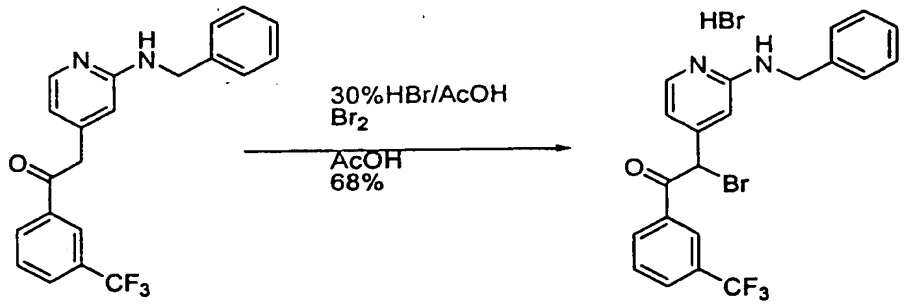


61ml (61 mmoles) of 1.0 M Sodium bis(trimethylsilyl)amide in tetrahydrofuran was added drop-wise to a solution of 8.97g (30.07 mmoles) of the N-Boc-2-benzylamino-4-methylpyridine and 6.58g (30.07 mmoles) of ethyl 3-trifluoromethylbenzoate in 60ml tetrahydrofuran by addition funnel under nitrogen atmosphere. After eighteen hours the reaction was quenched with saturated ammonium chloride solution, and the solvent removed *in vacuo*. The residue was extracted into 300ml of ethyl acetate and washed 2x200ml water, 1x100ml brine, dried over sodium sulfate, filtered and concentrated *in*

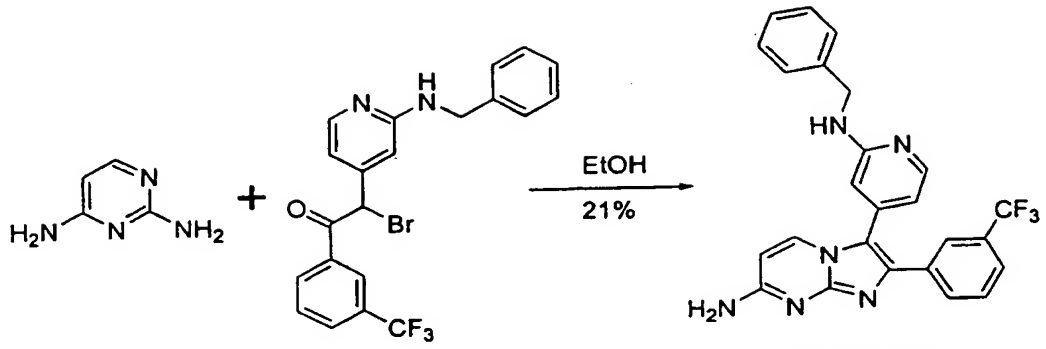
vacuo to give a brown oil. Column chromatography using 5:1 hexane/ethyl acetate afforded the 10.92g of product as a thick yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.59 (1H, s), 5.11 (2H, s), 4.62 (2H, s), 1.33 (9H, s).



10.92g (23.21 mmoles) of the protected amine was refluxed in 100ml tetrahydrofuran containing 20ml of 6M HCl solution for 1hour, cooled, diluted with 220ml water and extracted in 2x250ml ethyl acetate. The organic layers were separated, combined, washed with 200ml water, 2x100ml brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 7.91g of a viscous red oil. MH^+=371.



1.30ml (6.61 mmoles) of 30% hydrogen bromide in acetic acid was added to 2.33g (6.29 mmoles) of the ketone in 10ml glacial acetic acid. A solution of 0.35ml (6.79 mmoles) of bromine in 1.65ml glacial acetic acid was added drop-wise and the reaction heated to 60°C for one hour, cooled to room temperature, and diluted with ether. The oily residue that formed was washed with ether to give 2.27g (4.28 mmoles) of the crude bromide. MH^+=450.



Compound 8

A solution of 1.89g (17.13 mmoles) of 2,4-diaminopyrimidine in 20ml ethanol was heated to 80°C. A solution of 2.27g (4.28 mmoles) of the crude bromide in 50ml ethanol was added drop-wise by addition funnel. The reaction was stirred at 80°C for one hour then cooled to room temperature. Approximately one-half of the solvent was removed *in vacuo*. Upon cooling to room temperature the reaction was filtered. The filtrate was concentrated *in vacuo*, diluted with 250ml ethyl acetate and washed 2x100ml 0.5M sodium hydroxide solution, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a red-brown oil. Column chromatography using 2% methanol in ethyl acetate afforded 0.4161g of Compound 8 (Imidazo[1,2-*a*]pyrimidin-7-amine, 3-[2-[(phenylmethyl)amino]-4-pyridinyl]-2-[3-(trifluoromethyl)phenyl]-) as an off-white solid. MH^+=461.

Example 2
1-Phenyl-2-(4-pyridinyl)-ethanone and 1-Phenyl-2-bromo-2-(4-pyridinyl)-ethanone

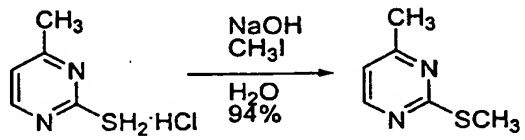
1.0M Sodium bis(trimethylsilyl)amide (40 mL, 0.04 mol) in tetrahydrofuran was added drop-wise to a solution of 1.8g (0.02 mol) of 4-picoline and 3.0 g (0.02 mol) of ethyl benzoate in 60ml tetrahydrofuran by addition funnel under nitrogen atmosphere. After eighteen hours the reaction was quenched with saturated ammonium chloride solution, and the solvent removed *in vacuo*. The residue was extracted into 100ml of ethyl acetate and washed 2x200ml water, 1x100ml brine, dried over sodium sulfate, filtered and

concentrated *in vacuo* to give an oil. Trituration with ether gives 1.6g of the product 1-phenyl-2-(4-pyridinyl)-ethanone. MH+ 198.

1.8 ml (8.9 mmoles) of 35% hydrogen bromide in acetic acid was added to 1.6g (8.1 mmol) of the ketone in 10ml glacial acetic acid. A solution of 0.46ml (8.9 mmol) of bromine in 1.65ml glacial acetic acid was added drop-wise and the reaction heated to 60°C for one hour, cooled to room temperature, and diluted with ether. The solid that formed was washed with ether to give 2.5g of the bromide as the HBr salt of 1-phenyl-2-bromo-2-(4-pyridinyl)-ethanone. MH^+=276.

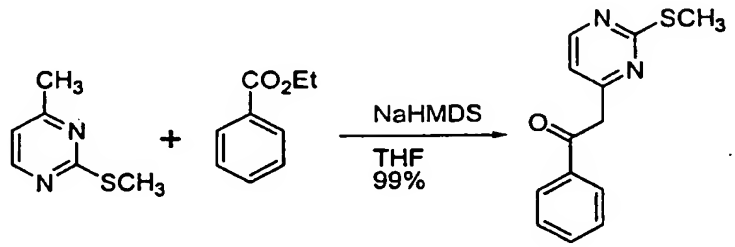
Example 3
Imidazo[1,2-*a*]pyrimidin-7-amine, 2-phenyl-3-(4-pyridinyl)

A solution of 1.2g (11 mmoles) of 2,4-diaminopyrimidine in 10ml of ethanol was heated to 80°C. A solution of 1.0g (2.8 mmol) of the bromide in 20ml of ethanol was added drop-wise by addition funnel. The reaction was stirred at 80°C for 3 hours then cooled to room temperature. Approximately one-half of the solvent was removed *in vacuo*. Upon cooling to room temperature the reaction was filtered. The filtrate was concentrated *in vacuo*, diluted with 250ml ethyl acetate and washed with 2x100ml 0.5M sodium hydroxide solution, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a red-brown oil. Trituration of the residue with EtOAc, followed by filtration gave 0.108g of Compound 5 as an off-white solid. MH^+=288.

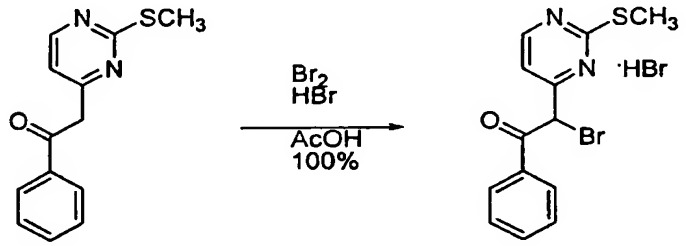


13.23g (93.2 mmoles) of Iodomethane was added drop-wise by syringe to a solution of 13.38g (84.73 mmoles) of 2-mercapto-4-methylpyrimidine hydrochloride and 7.46g (186.4 mmoles) sodium hydroxide in 120ml of water. After 2 hours the reaction was extracted with 2x125ml dichloromethane. The organic layers were separated, combined, dried over

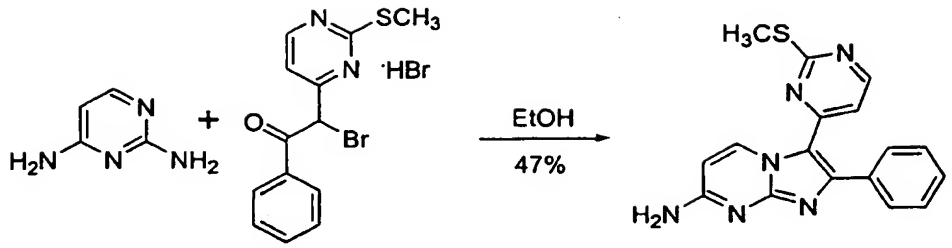
Na_2SO_4, filtered, and concentrated *in vacuo* to give 11.14g (79.45 mmoles) of 4-methyl-2-(methylthio)pyrimidine as a red oil. MH^+=140.9.



86ml (86 mmoles) of 1.0M sodium bis(trimethylsilyl)amide in tetrahydrofuran was added drop-wise by addition funnel to a solution of 6.03g (43 mmoles) 4-methyl-2-(methylthio)pyrimidine and 6.46g (43 mmoles) ethyl benzoate in 86 ml tetrahydrofuran under a nitrogen atmosphere. After 2 hours the reaction was quenched with saturated ammonium chloride solution. Most of the tetrahydrofuran was removed *in vacuo*. The residue was diluted with 400 ml ethyl acetate and 200 ml water. The organic layer was separated and washed 2x100ml saturated sodium chloride solution, separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 10.45g (42.77 mmoles) of 2-[2-(methyl thio)pyrimidin-4-yl]-1-phenylethanone as a viscous red-brown oil that solidified upon standing. MH^+=244.9.

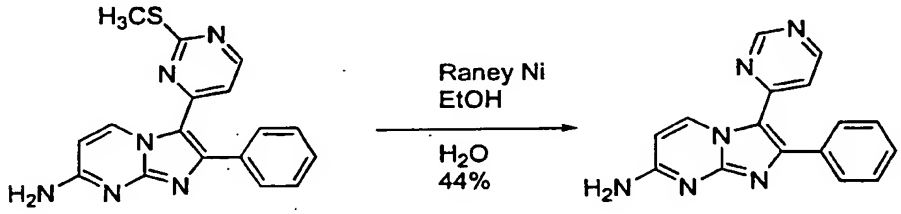


9ml (44.91 mmoles) of 30% hydrogen bromide in acetic acid was added to 10.45g (42.77 mmoles) of the ketone in 80ml glacial acetic acid. A solution of 2.40ml (46.19 mmoles) of bromine in 2.60ml glacial acetic acid was added drop-wise and the reaction heated to 60°C for 45 minutes, cooled to room temperature, and diluted with ether. The resultant slurry was filtered and washed with ether and dried *in vacuo* to give 18.06g (44.69 mmoles) of the crude bromide. MH^+=324.9.



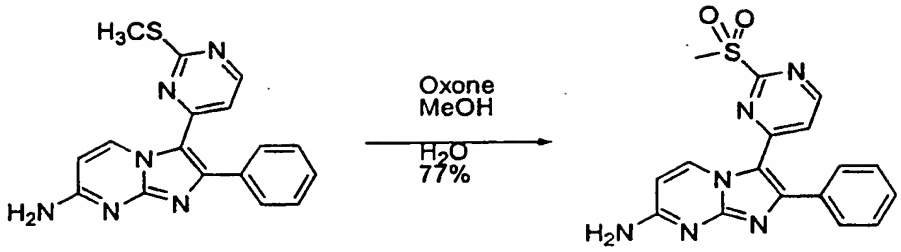
Compound 15

A solution of 18.83g (171.08 mmoles) of 2,4-diaminopyrimidine in 150ml ethanol was heated to 80°C. A solution of 18.06g (42.77 mmoles) of the crude bromide in 350ml ethanol was added drop-wise by addition funnel. The reaction was stirred at reflux for two hours. Upon cooling to room temperature the reaction was filtered. The precipitate was stirred in 150ml of 0.5M sodium hydroxide solution. The precipitate was collected by filtration, washed with water, ether and hexane to give 6.72g (21.1 mmoles) of the product as a light yellow solid. MH^+=334.9.



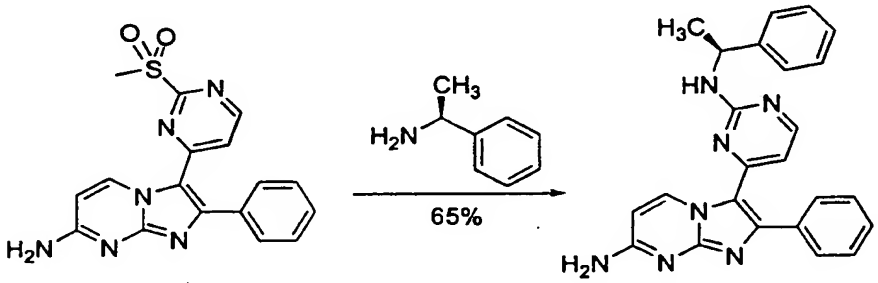
Compound 15 Compound 16

A mixture of 0.60g (1.79 mmoles) of the thiomethylpyrimidine, approximately 4 ml of a 50% Raney Nickel in water solution, 40ml ethanol and 20ml water was refluxed for eighteen hours under a nitrogen atmosphere. The reaction was cooled to room temperature and filtered through celite. The celite was washed with ethanol. The combined filtrates were concentrated *in vacuo*. The residue was collected by trituration with ethanol, collected by filtration and washed with ether to give 0.2310g of the pyrimidine as a yellow solid (Compound 16). MH^+=289.0.



Compound 15 Compound 17

A solution of 8.28g (13.46 mmoles) of oxone in 75ml water was added drop-wise by addition funnel to 1.50g (4.49 mmoles) of the thiomethyl pyrimidine in 77ml methanol. The resultant slurry was stirred at room temperature for eighteen hours, filtered, and the filtrate concentrated *in vacuo* to remove the methanol. The residue was diluted with 100ml water and neutralized with solid sodium bicarbonate. The resultant slurry was filtered and the precipitate washed with water, ether, and dried to give 1.27g (3.46 mmoles) of the methylsulfone pyrimidine as a yellow solid (Compound 17). MH^+=367.0.



Compound 17 Compound 19

A mixture of 0.55g (1.5 mmoles) of the methylsulfone pyrimidine and 1.82g (15 mmoles) of (S)-(-)-α-methylbenzylamine was heated at 140°C for 30 minutes, cooled to room temperature, diluted with 100ml ethyl acetate and washed 3x50ml water, 1x50ml saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a yellow oil. Column chromatography using 100% ethyl acetate as eluent afforded 0.3977g (0.98 mmoles) of the product as a light yellow solid (Compound 19). MH^+=408.1.

B. Assays

Example 4
Assays for inhibition of p38

The biological activities of certain compounds of the invention were demonstrated by *in vitro* and *in vivo* assays. As discussed previously, agents which inhibit the activity of the enzyme p38 inhibit the production of the inflammatory cytokines TNF-α and IL-1β.

Select compounds of the invention are listed in Table 1, which provides mass spectral data as well as data showing each compound's ability to inhibit p38 as shown by inhibition of TNF-α production. The assays by which such data was generated are described below.

Table 1

Compounds tested for their ability to inhibit p38 as shown by the inhibition of TNF-α production

Compound No.	MS ci (M + 1)	LPS/PBMC IC_{50} nM (TNF-α)	Mouse % Inhibition TNF-α production 10 mg/kg
1	306	49	100
2	306	55	100
3	356	333	26
4	340	21	100
5	288	55	100
6	411	6	42
7	356	35	99
8	461	4	19
9	476	0.5	97
10	353	37	68
11	403	27	38
12	353	10	51
13	357	278	85
14	372	8	63
15	335	28	23

16	289	304	73
17	367	3414	-
18	435	520	10
19	408	0.40	100
20	424	14	-
21	425	2	97
22	432	1	74
23	319	90	87
24	307	199	91
25	322	162	47

PBMC Whole Cell Assay

Representative compounds of the present invention were tested in an *in vitro* whole cell assay using peripheral blood mononuclear cells ("PBMC's") which were obtained from human blood as follows. Freshly obtained venous blood was anticoagulated with heparin, diluted with an equal volume of phosphate buffered saline ("PBS") and placed in a sterile tube or other container. Aliquots (30 mL) of this mixture were transferred to centrifuge tubes which were underlaid with Ficoll-Hypaque (15 mL). The prepared tubes were centrifuged at 400 x g without braking for 30 min at room temperature. Approximately 1/2 to 2/3 of the platelet layer above the mononuclear cell band was removed with a pipette. The majority of the mononuclear cell layer was carefully removed using a pipette and these PBMC's were diluted with PBS and spun at 600 x g for 15 min. The resulting PBMC's were washed with another portion of PBS and spun at 400 x g for 10 min at room temperature. The recovered pellets were diluted in low endotoxin RPMI/1% FCS culture medium and gave a cell concentration of 0.5-2.0 X 10^6 PMBC/mL. A small volume of the suspension was removed for counting on a hemocytometer and the remaining preparation was centrifuged at 200 x g for 15 min at room temperature. The recovered pelleted PMBC's were re-suspended in RPMI/1% FCS to a concentration of 1.67 x 10^6/mL.

To run the assay, the PBMC suspension (180 µL) was transferred to duplicate wells of a 96-well flat-bottom microtiter plate and incubated for 1 h

at 37°C. A solution of test compound (10 μL, prepared at 20 x the desired final concentration) was added to each well and the plate was incubated for 1 h at 37°C. A solution (10 μL) of LPS in RPMI/1% FCS (200 ng/mL) was added and the wells were incubated overnight at 37°C. The supernate (100 μL) was removed from each well and diluted with RPMI/1% FCS (400 μL). The samples were analyzed for TNF-α using a commercial ELISA kit (Genzyme). Data are shown in Table 1 above.

In Vivo Rodent Assay

The ability of the compounds of Formula I to inhibit LPS-induced TNF-α production was demonstrated in the following *in vivo* rodent assays. Mice (BALB/cJ females, Jackson Laboratories) were fasted for 30 min. prior to oral dosing with 5-10 mL/kg of a test compound at 5-50 mg/kg. Thirty minutes after dosing, the animals were injected intraperitoneally with LPS at 1 mg/kg and returned to their cages for 1 h. Animals were anesthetized by CO_2, exsanguinated by cardiac puncture and whole blood collected (0.1-0.7 mL). The blood was allowed to clot and serum was transferred to a centrifuge tube. This sample was centrifuged, and serum was collected, aliquoted, and frozen at -80°C. Samples were tested by commercial ELISA's for TNF-α (Endogen for mouse TNF-α). The % inhibition of the test compounds was calculated by the following formula: % inhibition = [1 - (sample-BKG)/(CTRL-BKG)] x 100. Data are shown in Table 1 above.

Recombinant p38 Assay

Compounds of the invention were measured for their ability to inhibit the activity of p38 by the following *in vitro* assay. A solution (38 μL) of purified recombinant p38 (where the amount of enzyme was determined empirically considering the linear range of the assay and the acceptable signal to noise ratio; 6xHis-p38 expressed in *E.coli*), myelin basic protein substrate (also determined empirically), and a buffer of pH 7.5 (Hepes: 25 mM; $MgCl_2$: 10 mM; $MnCl_2$: 10 mM) were added to 92 wells of a 96-well round bottom polypropylene plate. The remaining wells were used for control ("CTRL") and background ("BKG"). The CTRL was prepared with the enzyme, substrate

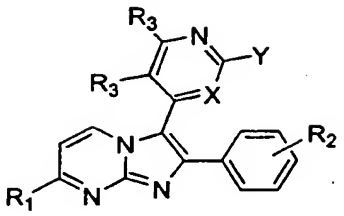
buffer and 21% DMSO, and the BKG was prepared with substrate buffer and 2% DMSO. A solution (12 μL) of the test compound in DMSO (compounds were diluted to 125 μM in 10% DMSO/H_2O and assayed at 25 μM where the final DMSO concentration was 2%) was added to the testing wells. The ATP/^{33}P-ATP solution (10 μL containing 50 μM unlabeled ATP and 1 μCi ^{33}P-ATP) was added to all wells and the completed plates were mixed and incubated at 30 °C for 30 min. Ice-cold 50 % TCA/10 mM sodium phosphate (60 μL) were added to each well and the plates were kept on ice for 15 min. The contents of each well were transferred to the wells of a 96-well filterplate (Millipore, MultiScreen-DP) and the filterplate was placed on a vacuum manifold, fitted with a waste collection tray. The wells were washed five times with 10% TCA/10 mM sodium phosphate (200 μL) under vacuum. MicroScint-20 scintillant was added, the plates were sealed using Topseal-S sheets and counted in a Packard TopCount scintillation counter using a ^{33}P liquid program with color quench correction, where the output is in color quench-corrected cpm. Although compounds were initially tested at 10 μM, if warranted the compounds were tested at 4-fold increments above and below that concentration. In addition, IC_{50}'s were calculated for some compounds using the Deltagraph 4-parameter curve-fitting program. No data are shown.

In Vitro IL-1β Assay

The ability of compounds of the invention to inhibit IL-1β production may be determined by the following *in vitro* assay. Plastic-adherent cells are prepared from PBMC's. Briefly, PBMC's are added to the wells of a 96-well plate as above, incubated for 1 h at 37°C, and the adherent cells prepared by gently resuspending the non-adherent cells with a pipetor, removing and discarding them and gently washing the wells 3 times with 200 μL culture medium. Additional culture medium (180 μL) is added to the wells after the final wash. Compound addition, LPS stimulation, incubation and supernate harvest are the same as for TNF-α. Supernates are assayed for interleukin-1β using a commercial ELISA (Genzyme). No data are shown.

What is claimed is

1. A compound of Formula I,



Formula I

or a pharmaceutically acceptable salt thereof, wherein

(a) R_1 is selected from the group consisting of NH_2, C_{1-5}alkylamino, diC_{1-5}alkylamino, hydroxy, C_{1-5}alkoxy, phenylmethylamino, heterocyclylmethyl, C_{1-5}alkylcarbonylamino, and substituted phenylcarbonylamino, wherein

said phenylmethylamino and heterocyclylmethyl may be substituted on its phenyl moiety by one or more members selected from the group consisting of halogen, C_{1-5}alkyl, C_{1-5}alkoxy, arylC_{1-3}alkylamino, R′R″NCH=N- and OR‴, the R′, R″ and R‴ being independently selected from H, C_{1-5}alkyl, phenylmethyl, substituted phenylmethyl, α-alkyl-phenylmethyl, substituted α-alkyl-phenylmethyl, heterocyclylmethyl, and substituted heterocyclylmethyl;

(b) Y is selected from the group consisting of H, halogen, heterocycle, OR_4, SR_4, NR_4 and NR_4R_5, wherein

R_4 and R_5 are independently selected from H, heterocyclyl, C_{3-5} carbocycle, phenyl, α-alkyl-phenylC_{1-5}alkyl, straight or branched alkyl optionally substituted with R, NR, $N(R)_2$, C_{3-5} carbocycle, phenyl or substituted phenyl, wherein (i) R is H, halogen, C_{1-5} alkyl, phenyl methyl, substituted phenyl methyl, SO_2Ph, pyridyl, or pyridyl methyl, and (ii) said phenyl, heterocyclyl, and α-alkyl-phenylC_{1-5}alkyl may be

substituted by one or more members selected from the group consisting of halogen, C_{1-5}alkyl, C_{1-5}alkoxy, arylC_{1-3}alkylamino, phenyl methyl, substituted phenyl methyl, R'R''NCH=N- and OR''' as defined in (a) hereof;

(c) R_2 is one to five members independently selected from the group consisting of halogen, trifluoromethyl, -NCH_2PH, C_{1-5}alkyl, and C_{1-5}alkoxy;

(d) R_3 is H or, taken together, an aromatic ring; and

(e) X is N or CH.

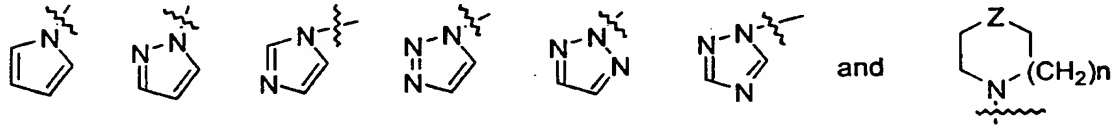
2. The compound of Claim 1, wherein X is CH.

3. The compound of Claim 1, wherein R_1 is NH_2.

4. The compound of Claim 1, wherein Y is NR_4 and R_4 is phenylmethyl.

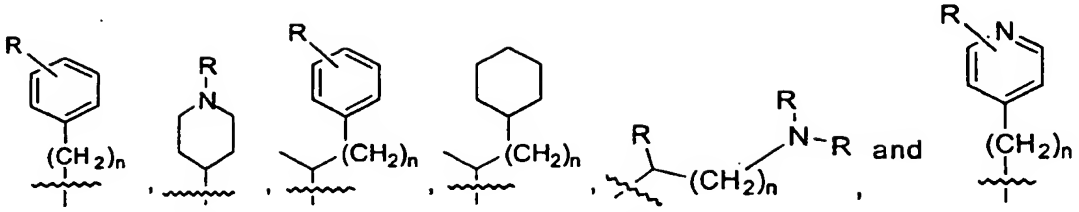
5. The compound of Claim 1, wherein R_2 is a member selected from the group consisting of halogen, trifluoromethyl, -NCH_2PH and C_{1-5}alkoxy.

6. The compound of Claim 1, wherein Y is selected from the group consisting of



wherein Z is -CH_2-, -O_2S-, -O-, -N(R)-, -OS-, or S; R is H, halogen, C_{1-5} alkyl, phenylmethyl, substituted phenylmethyl, SO_2Ph, pyridyl, or pyridylmethyl; and n is 0-5.

7. The compound of Claim 1 wherein R_4 is selected from



wherein each R can be the same as or different and is independently selected from H, halogen, C_{1-5} alkyl, phenylmethyl, substituted phenylmethyl, SO_2Ph, pyridyl and pyridylmethyl, and n is 0-5.

8. The compound of Claim 1 which is 2-(3-chloro-4-fluorophenyl)-3-(4-pyridinyl)-imidazo[1,2-*a*]pyrimidin-7-amine.

9. The compound of Claim 1 which is 2-phenyl-3-(4-pyridinyl)-imidazo[1,2-*a*]pyrimidin-7-amine.

10. The compound of Claim 1 which is 2-(4-fluorophenyl)-3-[2-[(phenylmethyl)amino]-4-pyridinyl]-imidazo[1,2-*a*]pyrimidin-7-amine.

11. The compound of Claim 1 which is 3-(4-pyridinyl)-2-[3-(trifluoromethyl) phenyl]-imidazo[1,2-*a*]pyrimidin-7-amine.

12. The compound of Claim 1 which is 3-[2-[(phenylmethyl)amino]-4-pyridinyl]-2-[3-(trifluoromethyl)phenyl]-imidazo[1,2-*a*]pyrimidin-7-amine.

13. The compound of Claim 1 which is 2-(4-fluorophenyl)-3-(4-quinolinyl)-imidazo[1,2-*a*]pyrimidin-7-amine.

14. The compound of Claim 1 which is 2-(3-chlorophenyl)-3-(4-pyridinyl) imidazo[1,2-*a*]pyrimidin-7-amine.

15. The compound of Claim 1 which is 2-(4-fluorophenyl)-3-[2-(methylthio)-4-pyrimidinyl]imidazo[1,2-*a*]pyrimidin-7-amine.

16. The compound of Claim 1 which is 3-[2-(methylthio)-4-pyrimidinyl]-2-[3-(trifluoromethyl)phenyl]imidazo[1,2-*a*]pyrimidin-7-amine.

17. The compound of Claim 1 which is 2-(3-fluorophenyl)-3-[2-(methylthio)-4-pyrimidinyl]imidazo[1,2-*a*]pyrimidin-7-amine.

18. The compound of Claim 1 which is 3-(4-pyrimidinyl)-2-[3-(trifluoromethyl) phenyl]imidazo[1,2-*a*]pyrimidin-7-amine.

19. The compound of Claim 1 which is 3-[2-(methylthio)-4-pyrimidinyl]-2-phenylimidazo[1,2-*a*]pyrimidin-7-amine.

20. The compound of Claim 1 which is 2-phenyl-3-(4-pyrimidinyl)imidazo[1,2-*a*]pyrimidin-7-amine.

21. The compound of Claim 1 which is 3-[2-(methylsulfonyl)-4-pyrimidinyl]-2-phenylimidazo[1,2-*a*]pyrimidin-7-amine.

22. The compound of Claim 1 which is 3-[2-(methylsulfonyl)-4-pyrimidinyl]-2-[3-(trifluoromethyl)phenyl]imidazo[1,2-*a*]pyrimidin-7-amine.

23. The compound of Claim 1 which is 2-phenyl-3-[2-[[(1*s*)-1-phenylethyl] amino]-4-pyrimidinyl]imidazo[1,2-*a*]pyrimidin-7-amine.

24. The compound of Claim 1 which is 3-[[[(4-methoxyphenyl)methyl]amino]-4-pyrimidinyl]-2-phenylimidazo[1,2-*a*]pyrimidin-7-amine.

25. The compound of Claim 1 which is 3-(2-methoxy-4-pyrimidinyl)-2-phenylimidazo[1,2-*a*]pyrimidin-7-amine.

26. The compound of Claim 1 which is 2-(4-fluorophenyl)-3-(4-pyrimidinyl) imidazo[1,2-*a*]pyrimidin-7-amine.

27. The compound of Claim 1 which is 2-(3-fluorophenyl)-3-(4-pyridinyl)-imidazo[1,2-*a*]pyrimidin-7-amine.

28. The compound of Claim 1 which is 2-(4-fluorophenyl)-3-(4-pyridinyl)-imidazo[1,2-*a*]pyrimidin-7-amine.

29. The compound of Claim 1 which is 3-[2-[[(1*S*)-1-phenylethyl]amino]-4-pyrimidinyl]-2-[3-(trifluoromethyl)phenyl]imidazo[1,2-*a*]pyrimidin-7-amine.

30. The compound of Claim 1 which is 2-phenyl-3-[2-(1-piperidinyl)-4-pyrimidinyl]imidazo[1,2-*a*]pyrimidin-7-amine.

31. The compound of Claim 1 which is 3-[2-[[(1*S*)-1-cyclohexylethyl]amino]-4-pyrimidinyl]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyrimidin-7-amine.

32. The compound of Claim 1 which is 2-(4-Fluorophenyl)-3-[3-[[(1S)-1-phenylethyl]amino]-4-pyridinyl]imidazo[1,2-a]pyrimidin-7-amine.

33. The compound of Claim 1 which is 3-(2-Bromo-4-pyridinyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyrimidin-7-amine.

34. The compound of Claim 1 which is 3-(2-Bromo-4-pyridinyl)-2-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyrimidin-7-amine.

35. A pharmaceutical composition comprising the compound of Claim 1 and a pharmaceutically acceptable carrier.

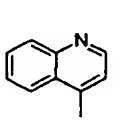
36. A method of treating a subject suffering from a condition whose alleviation is mediated by the reduction of inflammatory cytokines whose actions contribute to the condition, which method comprises administering to the subject a therapeutically effective dose of the instant pharmaceutical composition.

37. A method of inhibiting in a subject the onset of a condition whose alleviation is mediated by the reduction of inflammatory cytokines whose actions contribute to the condition, which method comprises administering to the subject a prophylactically effective dose of the instant pharmaceutical composition.

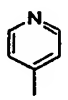
38. The method of Claim 36 or 37, wherein the condition is selected from the group consisting of rheumatoid arthritis, inflammatory bowel disease, septic shock, osteoporosis, osteoarthritis, neuropathic pain, HIV replication, HIV dementia, viral myocarditis, insulin-dependent diabetes, non-insulin-dependent diabetes, periodontal disease, restenosis, alopecia areta, T-cell depletion in HIV infection or AIDS, psoriasis, acute pancreatitis, allograft rejection, allergic inflammation in the lung, atherosclerosis, multiple sclerosis, cachexia, Alzheimer's disease, stroke, Crohn's disease, ischemia, congestive heart failure, pulmonary fibrosis, hepatitis, glioblastoma, Guillain-Barre Syndrome, and systemic lupus erythematosus.

39. The method of Claim 38, wherein the condition is rheumatoid arthritis.

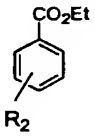
40. A process for preparing the compound of Claim 1 wherein R_1 is NH_2, X is CH, and R_5 and Y are H, which process comprises:



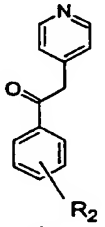
1a



1a'



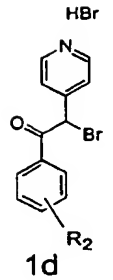
1b



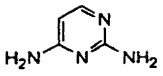
1c

(a) reacting compound 1a or 1a' with compound 1b in the presence of NaHMDS and THF to form compound 1c;

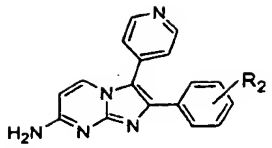
(b) converting compound 1c to compound 1d in the presence of 30% HBr/AcOH, Br_2, and AcOH; and



1d



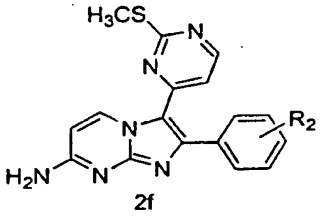
1e



1f

(c) reacting compound 1d with compound 1e in the presence of EtOH to form compound 1f.

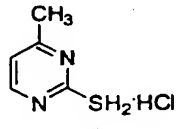
41. A process for preparing the compound of Claim 1 having the structure 2f



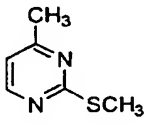
2f

which comprises:

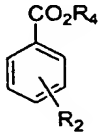
(a) converting compound 2a in the presence of NaOH and CH_3I to compound 2b;



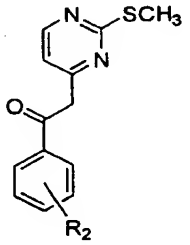
2a



2b



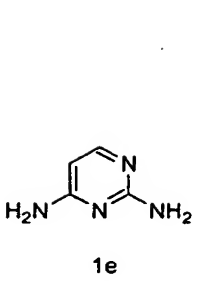
2c

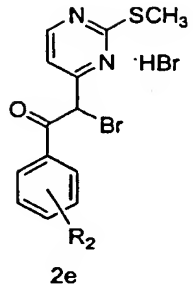


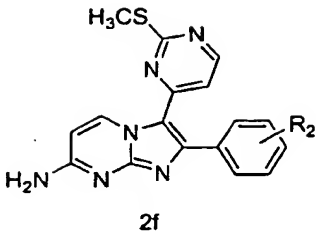
2d

(b) reacting compound 2b with compound 2c in the presence of NaHMDS and THF to form compound 2d;

(c) converting compound 2d in the presence of HBr, Br_2, and AcOH to compound 2e; and

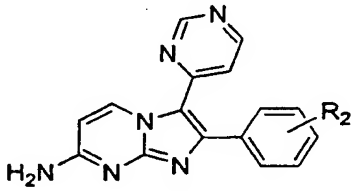

1e


2e


2f

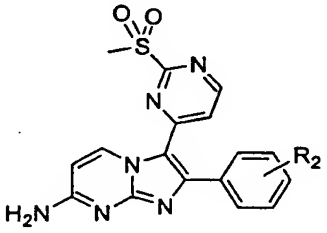
(d) reacting compound 2e with compound 1e in the presence of EtOH to form compound 2f.

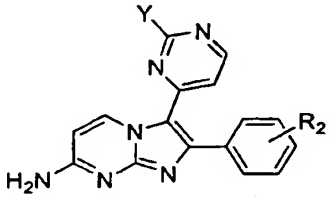
42. The process of Claim 41, which further comprises converting compound 2f in the presence of Raney, Ni, and EtOH to compound 2g.


2g

43. The process of Claim 41, which further comprises:

(a) converting compound 2f to compound 2h in the presence of oxone and MeOH; and

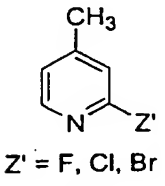

2h


2i

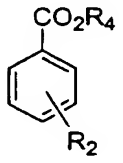
(b) reacting the compound of Formula 2h with a compound of Y , wherein Y is halogen, heterocycle, OR_4, SR_4, NR_4, or NR_4R_5, to form a compound of Formula 2i.

44. A process for preparing the compound of Claim 1 wherein X is CH, and Y is halogen, heterocycle, OR_4, SR_4, NR_4 or NR_4R_5, which process comprises:

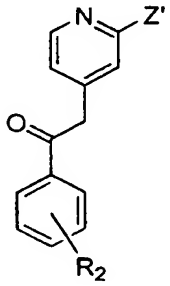
(a) reacting a compound of Formula 3a with a compound of Formula 3b to form a compound of 3c in the presence of NaHMDS and THF;



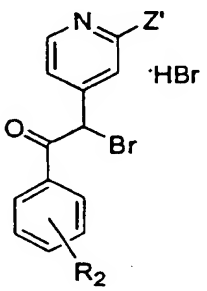
3a



3b



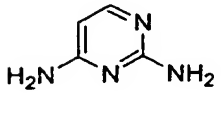
3c



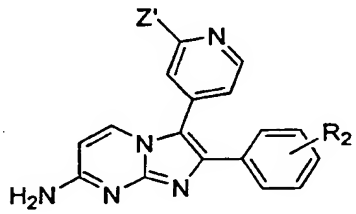
3d

(b) converting the compound of Formula 3c to a compound of Formula 3d in the presence of HBr, Br_2 and AcOH;

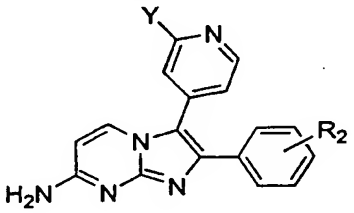
(c) reacting the compound of Formula 3d with Compound 1e to form a compound of Formula 3e in the presence of EtOH; and



1e



3e

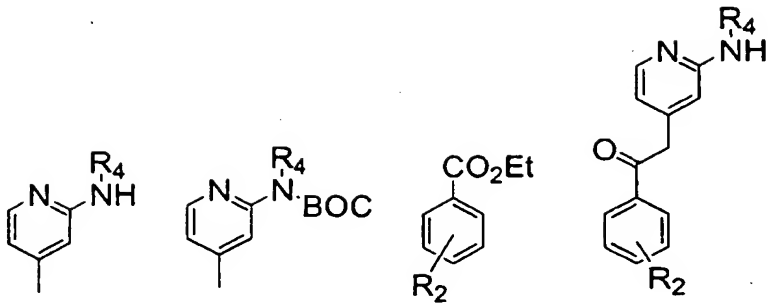


3f

(d) reacting the compound of Formula 3e with Y to form a compound of Formula 3f.

45. A process for preparing the compound of Claim 1 wherein X is CH and Y is NR_4, which process comprises:

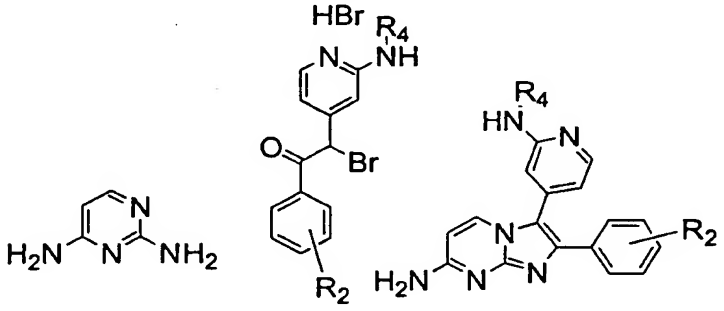
(a) converting the compound of Formula 4a in the presence of $(BOC)_2O$ and tBuOH to a compound of Formula 4b;



4a 4b 4c 4d

(b) reacting the compound of Formula 4b with a compound of Formula 4c in the presence of NaHMDS and HCl to form a compound of Formula 4d;

(c) converting the compound of Formula 4d in the presence of 30% HBr/AcOH, Br_2 and AcOH to a compound of Formula 4e; and



1e 4e 4f

(d) reacting the compound of Formula 4e with Compound 1e in the presence of EtOH to form a compound of Formula 4f.

INTERNATIONAL SEARCH REPORT

Interr ial Application No
PCT/US 00/29875

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/505 A61P19/02 A61P19/10 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 91 00092 A (SMITHKLINE BEECHAM) 10 January 1991 (1991-01-10) cited in the application page 27, line 29 -page 3, line 22; claims; examples ---	1-45
Y	WO 91 19497 A (SMITHKLINE BEECHAM) 26 December 1991 (1991-12-26) cited in the application page 9, line 8 - line 23; claims; examples ---	1-45
Y	WO 98 07425 A (SMITHKLINE BEECHAM) 26 February 1998 (1998-02-26) page 16, line 5 -page 17, line 10; claims; examples --- -/--	1-45

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 January 2001	16.01.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Helps, I

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/US 00/29875

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 01449 A (NOVARTIS ERFINDUNGEN WERWALTUNGSGESELLSCHAFT) 14 January 1999 (1999-01-14) page 23, line 12 -page 24, line 20; claims; examples	1-45

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir. .ational application No.
PCT/US 00/29875

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 36-39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

....ormation on patent family members

Interr ...al Application No
PCT/US 00/29875

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